



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Nelfinavir (NFV, Viracept) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

Formulations

Tablets: 250 mg and 625 mg

Dosing Recommendations

Note: The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV **no longer recommends** nelfinavir-based regimens for use in children due to inferior potency compared to other regimens.

Neonate and Infant Dose:

- Nelfinavir should not be used for treatment in children aged <2 years.

Pediatric Dose (Aged ≥2 Years):

- 45–55 mg/kg twice daily

Adolescent and Adult Dose:

- 1250 mg (five 250-mg tablets or two 625-mg tablets) twice daily

Selected Adverse Events

- Diarrhea
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Serum transaminase elevations

Special Instructions

- Administer nelfinavir with meal or light snack.
- If co-administered with didanosine, administer nelfinavir 2 hours before or 1 hour after didanosine.
- Patients unable to swallow nelfinavir tablets can dissolve the tablets in a small amount of water. Once tablets are dissolved, mix the cloudy mixture well and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure that the entire dose is consumed. Tablets can also be crushed and administered with pudding or other nonacidic foods.

Metabolism/Elimination

- Cytochrome P (CYP) 2C19 and 3A4 substrate
- Metabolized to active M8 metabolite
- CYP3A4 inhibitor

Drug Interactions (see also the [Adult and Adolescent Guidelines](#) and the [HIV Drug Interaction Checker](#))

- Metabolism:** Cytochrome P (CYP) 2C19 and 3A4 substrate and CYP3A4 inhibitor. Ritonavir boosting does not significantly increase nelfinavir concentrations, and co-administration of nelfinavir with ritonavir is not recommended.
- There is potential for multiple drug interactions with nelfinavir. Before administering nelfinavir, carefully review a patient's medication profile for potential drug interactions.

Major Toxicities

- More common:** Diarrhea (most common), asthenia, abdominal pain, rash, and lipid abnormalities.
- Less common (more severe):** Fat redistribution and exacerbation of chronic liver disease.

- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in patients with hemophilia, and elevations in transaminases.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of [updated resistance mutations](#) and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

Pediatric Use

Approval

Nelfinavir is approved by the Food and Drug Administration (FDA) for use in children aged ≥ 2 years. Given the higher variability of nelfinavir plasma concentrations in infants and younger children,^{1,2} nelfinavir is not approved for children aged < 2 years. Despite being FDA-approved for pediatric use, nelfinavir **is not recommended** for use in children and adolescents by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV, due to its limited efficacy and uncertain pharmacokinetics (PK).

Efficacy in Pediatric Clinical Trials

Nelfinavir used in combination with other antiretroviral (ARV) drugs has been extensively studied in children with HIV infection.³⁻¹⁰ In randomized trials of children aged 2 to 13 years receiving nelfinavir as part of triple combination therapy, the proportion of patients with HIV RNA < 400 copies/mL through 48 weeks of therapy has been quite variable, ranging from 26% to 69%. The antiviral response to nelfinavir is significantly less in children aged < 2 years than in older children.^{8,10,11} In clinical studies, virologic and immunologic response to nelfinavir-based therapy has varied according to the patient's age or prior treatment history, the number of drugs included in the combination regimen, and the dose of nelfinavir used.

Pharmacokinetics: Exposure-Response Relationships

Nelfinavir's relatively poor ability to control plasma viremia in infants and children in clinical trials may be related to its lower potency when compared with other ARV drugs, as well as highly variable drug exposure, metabolism, and poor palatability.¹²⁻¹⁴ The bioavailability of dissolved nelfinavir tablets is comparable to that of tablets swallowed whole.^{3,15}

Administration of nelfinavir with food increases nelfinavir exposure (area under the curve increases by up to five-fold) and decreases PK variability when compared to the fasted state. Nelfinavir plasma exposure may be even more unpredictable in pediatric patients than in adults due to the increased clearance of nelfinavir observed in children and difficulties in taking nelfinavir with sufficient food to improve bioavailability.

Nelfinavir is metabolized by multiple CYP450 enzymes, including CYP3A4 and CYP2C19. The variability of drug exposure at any given dose is much higher for children than for adults,¹⁶ which has been attributed—at least in part—to differences in the diets of children and adults. Two population PK studies of nelfinavir and its active metabolite, M8, describe the large intersubject variability observed in children.^{17,18} Furthermore, CYP2C19 genotype has been shown to affect nelfinavir PK and the virologic responses in children with HIV.¹²

Several studies have demonstrated a correlation between nelfinavir trough concentrations and virologic response. In both children and adults, an increased risk of virologic failure was associated with low nelfinavir drug exposure, particularly with a nelfinavir minimum plasma concentration (C_{\min}) < 1.0 mcg/mL.¹⁹⁻²¹

In a study of 32 children treated with a high dose of nelfinavir (a two-fold increase of the recommended dose), 80% of children with morning trough nelfinavir plasma concentration > 0.8 mcg/mL had HIV RNA concentrations < 50 copies/mL at Week 48, compared with only 29% of those with morning trough < 0.8 mcg/mL.²² Children in the group with $C_{\text{trough}} < 0.8$ mcg/mL were younger than the children in the group with $C_{\text{trough}} > 0.8$ mcg/mL (median ages in these groups were 3.8 years and 8.3 years, respectively).²² Therapeutic drug monitoring of nelfinavir plasma concentrations, with appropriate adjustments for low drug exposure, has been shown to improve virologic response in adults and children.^{18,19,23,24} Pediatric and

adolescent patients may require doses higher than those recommended in adults to achieve higher plasma nelfinavir exposure.

References

1. Capparelli EV, Sullivan JL, Mofenson L, et al. Pharmacokinetics of nelfinavir in human immunodeficiency virus-infected infants. *Pediatr Infect Dis J*. 2001;20(8):746-751. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11734735>.
2. Mirochnick M, Stek A, Acevedo M, et al. Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr*. 2005;39(2):189-194. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15905735>.
3. Aboulker JP, Babiker A, Chaix ML, et al. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS*. 2004;18(2):237-245. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15075541>.
4. King JR, Nachman S, Yorgev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J*. 2005;24(10):880-885. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16220085>.
5. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11880966>.
6. Krogstad P, Wiznia A, Luzuriaga K, et al. Treatment of human immunodeficiency virus 1-infected infants and children with the protease inhibitor nelfinavir mesylate. *Clin Infect Dis*. 1999;28(5):1109-1118. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10452644>.
7. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med*. 2004;350(24):2471-2480. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15190139>.
8. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet*. 2002;359(9308):733-740. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11888583&query_hl=42.
9. Resino S, Larru B, Maria Bellon J, et al. Effects of highly active antiretroviral therapy with nelfinavir in vertically HIV-1 infected children: 3 years of follow-up. Long-term response to nelfinavir in children. *BMC Infect Dis*. 2006;6:107. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16834769>.
10. Scherpbier HJ, Bekker V, van Leth F, Jurriaans S, Lange JM, Kuijpers TW. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics*. 2006;117(3):e528-536. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16481448>.
11. Nelfinavir [package insert]. Food and Drug Administration. 2011. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020778s035,020779s056,021503s017bl.pdf.
12. Saitoh A, Capparelli E, Aweeka F, et al. CYP2C19 genetic variants affect nelfinavir pharmacokinetics and virologic response in HIV-1-infected children receiving highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2010;54(3):285-289. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19890215>.
13. Wu H, Lathey J, Ruan P, et al. Relationship of plasma HIV-1 RNA dynamics to baseline factors and virological responses to highly active antiretroviral therapy in adolescents (aged 12–22 years) infected through high-risk behavior. *J Infect Dis*. 2004;189(4):593-601. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14767811&query_hl=31.
14. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med*. 2002;346(26):2039-2046. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12087139>.
15. Regazzi MB, Seminari E, Villani P, et al. Nelfinavir suspension obtained from nelfinavir tablets has equivalent

pharmacokinetic profile. *J Chemother*. 2001;13(5):569-574. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11760223>.

16. Gatti G, Castelli-Gattinara G, Cruciani M, et al. Pharmacokinetics and pharmacodynamics of nelfinavir administered twice or thrice daily to human immunodeficiency virus type 1-infected children. *Clin Infect Dis*. 2003;36(11):1476-1482. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12766843>.
17. Hirt D, Urien S, Jullien V, et al. Age-related effects on nelfinavir and M8 pharmacokinetics: a population study with 182 children. *Antimicrob Agents Chemother*. 2006;50(3):910-916. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16495250>.
18. Crommentuyn KM, Scherpbier HJ, Kuijpers TW, Mathot RA, Huitema AD, Beijnen JH. Population pharmacokinetics and pharmacodynamics of nelfinavir and its active metabolite M8 in HIV-1-infected children. *Pediatr Infect Dis J*. 2006;25(6):538-543. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16732153>.
19. Burger DM, Hugen PW, Aarnoutse RE, et al. Treatment failure of nelfinavir-containing triple therapy can largely be explained by low nelfinavir plasma concentrations. *Ther Drug Monit*. 2003;25(1):73-80. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12548148&query_hl=15.
20. Gonzalez de Requena D, Nunez M, de Mendoza C, Jimenez-Nacher I, Soriano V. Nelfinavir plasma concentrations in patients experiencing early failure with nelfinavir-containing triple combinations. *AIDS*. 2003;17(3):442-444. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12556700>.
21. Pellegrin I, Breilh D, Montestruc F, et al. Virologic response to nelfinavir-based regimens: pharmacokinetics and drug resistance mutations (VIRAPHAR study). *AIDS*. 2002;16(10):1331-1340. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12131209>.
22. Burger DM, Bergshoeff AS, De Groot R, et al. Maintaining the nelfinavir trough concentration above 0.8 mg/L improves virologic response in HIV-1-infected children. *J Pediatr*. 2004;145(3):403-405. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15343199>.
23. Burger D, Hugen P, Reiss P, et al. Therapeutic drug monitoring of nelfinavir and indinavir in treatment-naive HIV-1-infected individuals. *AIDS*. 2003;17(8):1157-1165. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12819517>.
24. Fletcher CV, Brundage RC, Fenton T, et al. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther*. 2008;83(2):300-306. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17609682>.